IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	10/526,730
Confirmation No.	:	1144
Applicant	:	Evert Johannes BUNSCHOTEN et al.
Filed	:	September 16, 2005
Title	:	PHARMACEUTICAL APPLICATION OF 15- OR 16-SUBSTITUTED TESTOSTERONE ANALOGUES
Art Unit	:	1617
Examiner Name	:	Javanmard, Sahar
Attorney Docket Number	:	0470-050738

EXPERT'S DECLARATION UNDER 37 C.F.R. § 1.132

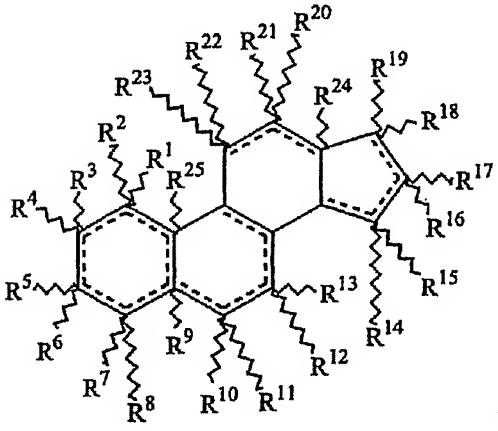
I, NIESCHLAG, Eberhard, declare as follows:

1. A detailed listing of my publications, together with details of my education, are given in my *curriculum vitae* which is attached as Exhibit A.

2. Based on my academic training and professional experience, I consider myself an expert in the field of androgen-related therapies and treatments, and I was such a person in 2002.

3. I have received a copy of the above-captioned application, which relates to a pharmaceutical oral dosage unit selected from a tablet, a capsule and a cachet, containing a steroid selected from 15-hydroxytestosterones, precursors thereof, mixtures thereof and precursors of said mixtures (claim 17) and further to a method of therapeutically treating androgen deficiency in a mammal comprising oral administration of the aforementioned oral dosage unit (claim 28).

4. I have received a copy of WO 01/23405 (Lardy) which describes a method to treat or prevent an androgen responsive disease in a subject, or to ameliorate one or more symptoms thereof, comprising administering to a subject, or delivering to the subject's tissues, an effective amount of a compound of formula 1 or 2



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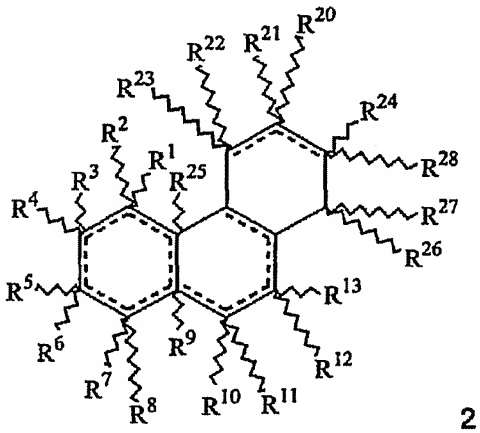

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5. I have also received a copy of US 2,793,216 (Murray) which describes 15-hydroxytestosterone and mentions that 15-hydroxytestosterone, 15-hydroxy-10-normethyltestosterone and their esters are useful as chemical intermediates and have pharmacological activity per se.

6. I have also received a copy of the Amendment filed on February 23, 2009, which I understand contains the currently pending claims. I understand that this patent application claims that the invention is:

- "a pharmaceutical oral dosage unit containing at least 10 μg of a steroid selected from the group consisting of 15-hydroxytestosterones, precursors thereof, mixtures thereof and precursors of said mixtures; and a pharmaceutically acceptable excipient, wherein said oral dosage unit is selected from the group consisting of a tablet, a capsule and a chachet, wherein the precursor of the hydroxytestosterones are derivatives of the hydroxytestosterone wherein a hydrogen atom of at least one hydroxyal group has been substituted by an acyl radical of a hydrocarbon carboxylic, sulfonic or sulfamic acid of 1-25 carbon atoms; tetrahydrofuranyl; tetrahydropyranal; or a straight or branched chain glycosydic residue containing 1-20 glycosidic unites per residue" (claim 17) and,

- "a method of therapeutically treating androgen deficiency ... comprising administering ... the oral dosage unit" described above (claim 28).

7. I have further received a copy of the Office Action that was issued by the USPTO in relation to the above referenced pending patent application on May 28, 2009. It is my understanding that in this particular Office Action the independent claims of the pending patent application that is the subject of this Declaration were rejected under 35 U.S.C. 103(a) (obviousness) as being unpatentable over Lardy in view of Murray.

8. In the aforementioned Office Action the following observations are made by the examiner on page 4:

- *It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed the compounds encompassed by formula 1 in oral formulations for the treatment of androgen responsive disease as taught by Lardy and employed 15-hydroxytestosterone. The motivation, provided by Murray, teaches that 15-hydroxytestosterones have pharmacological activity, therefore it would be obvious to one of ordinary skill in the art to formulate an oral dosage unit comprising 15-hydroxytestosterone.*
- *The fact that Lardy generally teaches the compounds for treating androgen responsive diseases and Murray specifically teaches the compounds as possessing pharmacological activity would motivate one of ordinary skill in the art to expect, with a reasonable degree of success, that 15-hydroxytestosterones would also have the potential to treat androgen deficient ailments.*

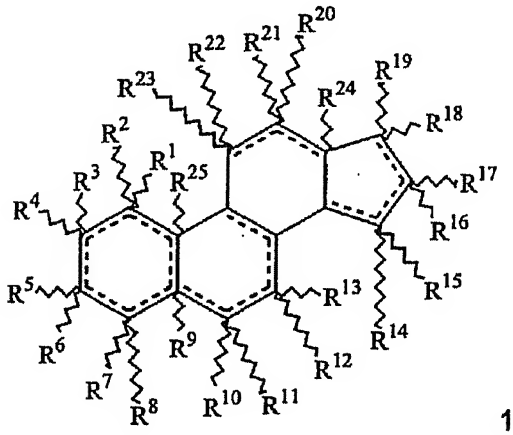
9. I have been asked to comment on my understanding of the state of the art prior to September 5, 2002, which I understand to be the priority date for the above referenced patent application. Particularly, I have been asked whether, prior to September 5, 2002, a person of ordinary skill in the art would have considered it obvious to use 15-hydroxytestosterone in oral formulations and whether the discovery that 15α-hydroxytestosterone and 15β-hydroxytestosterone are orally active androgens is unexpected and surprising.

10. It is my view that, prior to September 5, 2002, for the reasons presented below, it would not have been obvious to a person of ordinary skill in the art to employ 15-hydroxytestosterone in oral formulations. In my view, the Applicants were the first to

discover that 15α-hydrodxytestosterone as well as 15β-hydroxytestosterone can be used in pharmaceutical preparations as orally active androgens.

11. I declare that before September 5, 2002, I had no knowledge of any pharmacological application of 15-hydroxytestosterone. Furthermore, before September 5, 2002 I did not expect 15-hydroxytestosterone to be an orally active androgen.

12. Lardy teaches a method to treat or prevent androgen responsive disease by administering to a subject an effective amount of a compound of formula 1 or 2.



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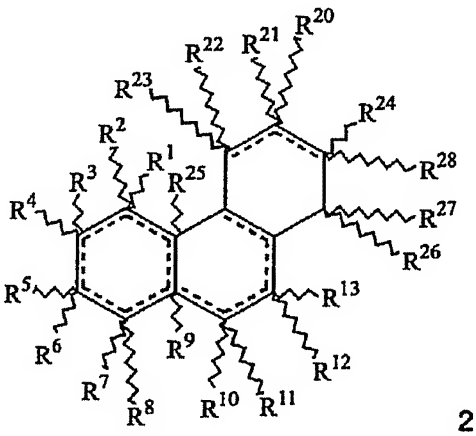

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Lardy specifies that in the above formula R^1-R^{28} independently are -H, -OR^{PR},-SR^{PR},-$N(R^{PR})_2$,-O-Si-$(R^A)_3$, -CN, -NO_2, -OSO_3H, -OPO_3H, an ester, a phosphoester, a phosphonoester, a sulfite ester, a sulfate ester, an amide, an amino acid, a peptide, an ether, a thioether, an acyl group, a carbonate, a carbamate, a slufonamide, a halogen, an optionally substituted alkyl group, an optionally substituted alkenyl group, an optionally substituted alkynyl group, an optionally substituted aryl moiety, an optionally substituted heterocycle, an optionally substituted heteroaryl moiety, an optionally substituted monosaccharide, an optionally substituted oligosaccharide, a nucleoside, a nucleotide, an oligonucleotide, a polymer, or, when two of R^1-R^{28} are linked to the same carbon atom, they independently comprise a double bond, such as =O, =S, $=CH_2$ or =N-OH, at one or more ring carbons, and provided that when one or more of the rings comprises a double bond, one of the variable groups that is bonded to the double bonded ring carbon is absent; each R^A independently is $C_{1\text{-}8}$. alkyl; each R^{PR} independently is -H or a protecting group; and the dotted lines are optional double bonds, provided that 2,3,4 or more of R^1-R^{28} are not hydrogen.

13. The aforementioned definition of a compound of formula 1 encompasses an innumerable number of different substances, including 15-hydroxytestosterone. In case of 15-hdyroxytestosterone in formula 1 R^1-R^{28} represents H, except that R^5 and R^6 together represent =O; R^{15} represents OH; R^{19} represents OH; and each of R^{24} and R^{25} represent methyl. Furthermore, the steroid skeleton of 15-hydroxytestosterone contains a single double between the carbon atoms carrying R^5 and R^6 and the carbon atom carrying R^7 and R^8.

14. Lardy mentions the possibility of oral administration of compounds according to formula 1 or 2. However, Lardy does not teach that the compounds of formula 1 or 2 are orally active and does not provide any example of a compound according to formula 1 or 2 that is orally active. Furthermore, the vast number of compounds according to formula 1 mentioned on pages 38-57, does not include 15-hydroxytestosterone.

15. It is my professional view that of the countless number of substances that are encompassed by formula 1 of Lardy at best only a minute fraction were expected to be orally active androgens. Hence, in my opinion Lardy would not have incited a person of ordinary skill in the art to randomly select a compound according to formula 1 and to employ it as an orally active substance in the treatment or prevention of androgen responsive disease. Since Lardy does not mention 15-hydroxytestosterone and also does not comprise any pointers to this particular hydroxysteroid, it is my view that Lardy *per se* would not have incited a person of ordinary skill in the art to employ 15-hydroxytestosterone as an orally active drug.

16. Unlike Lardy, Murray does mention 15-hydroxytestosterone. In column 3, lines 11-17 the following observations are made: *The 15-hydroxytestosterone, 15-hydroxy-10-normethyltestosterone and their esters are useful as chemical intermediates and have pharmacological activity per se. They have anabolic, antihypertensive, anti-bacterial and anti-fungal activity. They are additionally useful as emulsifying agents and to increase the solubility of known physiologically active steroids.* Murray, however, does not provide any data supporting this statement. Furthermore, Murray does not provide any suggestion that 15-hydroxytesterone is orally bioavailable.

17. To the best of my knowledge, besides Murray, which was published in 1957, there exist no publications providing data or other information about the pharmacological properties of 15-hydroxytestosterone.

18. It is my view that, irrespective of the teachings found in Lardy and Murray, at the time of the invention it would not have been obvious to a person of ordinary skill in the art to employ 15-hydroxytestosterone in oral formulations. This conclusion is based on the earlier observation that Lardy does not teach that the compounds of formula 1 are orally active, and that consequently a person of ordinary skill would not be motivated to employ the 15-hydroxytestosterone of Murray in oral formulations or in a method of treatment that employs oral administration.

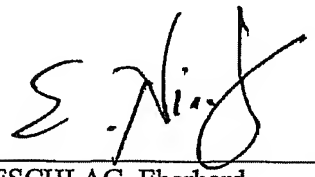
19. It is my view that a person of ordinary skill in the art would not be motivated by Lardy to anticipate, with a reasonably expectation of success, that 15-hydroxytestosterone is orally active. This conclusion is first of all based on the fact that a person of ordinary skill knows that despite extensive research efforts only a few orally active androgenic steroids had been identified at the time of the present invention. Hence a person of ordinary skill would deem the chance that a steroid encompassed by formula 1 of Lardy is an orally active androgen to be at best minute.

20. In addition, it is my view that a person of ordinary skill would question whether indeed 15-hydroxytestosterone has pharmacological activity, as asserted in Murray, given that Murray does not provide any data to substantiate this assertion and since in the 45 years between the publication of Murray and the date of the present invention no evidence for the pharmacological activity of 15-hydroxytestosterone has been published. Thus, a person of ordinary skill in the art would not be motivated, with a reasonable expectation of success, to employ a steroid that according to an unsubstantiated and unconfirmed assertion from 1957 has pharmacological activity, as an orally active androgen. In other words, it is my view that Lardy would not have motivated a person of ordinary skill to employ the 15-hydroxytestosterone of Murray as an orally active androgen.

21. Finally, I would like to add that it is my opinion that Applicants' discovery that 15α-hydroxytestosterone and 15β-hydroxytestosterone are orally active androgens could not be foreseen. Furthermore, if the medical use of these steroids is authorized, they may become a useful addition to the very small group of orally active androgens that is currently available for therapeutic treatment.

22. I have not been compensated for the execution of this declaration, or any time I spent relating to this declaration

23. I declare further that all statements made herein of my own knowledge are true and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application and any patent issuing thereon.



NIESCHLAG, Eberhard

17/9/2009

Date

3/2008

Curriculum vitae Prof. Dr. med. Dr. h. c. Eberhard Nieschlag, FRCP

Born 16.07.1941

1961-1967	Study of Medicine, University of Bonn and München
1967	Doctoral degree (Dr. med.), University of Bonn
1967-1968	Studies in Biochemistry at the University College London and training at the MRC-Unit in Edinburgh, Scotland
1968-1971	Department of Endocrinology, University Hospital Mainz, Germany
1971-1972	Reproduction Research Branch (Dr. M.B. Lipsett), NIH Bethesda, MD, USA
1972-1976	Department of Internal Medicine, University Hospital of Düsseldorf, Germany
1974	Reproductive Endocrinology Unit (Prof. E. Diczfalusy), Karolinska Sjukhuset Stockholm, Sweden
1975	Qualified as Specialist for Internal Medicine
1975	University teaching degree for Internal Medicine ("Habilitation"), University of Düsseldorf
1977	Qualified as Specialist for Clinical Endocrinology
1980 - 1989	Director, Max Planck Clinical Research Unit for Reproductive Medicine, Münster
1986 - 2007	Director, Institute of Reproductive Medicine of the University of Münster
2005	Qualified as Specialist for Andrology
1981-1985	President, International Society of Andrology
1985-1990	Chairman, WHO Steering Committee of the Task Force on the Regulation of Male Fertility
1990-1993	President, German Endocrine Society
1992-1998	President, European Academy of Andrology
1994-2001	Member, Executive Council, European Federation of Endocrine Societies (EFES)
1995-1999	Member, Executive Council, European Society for Human Reproduction (ESHRE)
1999-2001	Vice President, German Society of Reproductive Medicine
2002-2003	President, German Society of Reproductive Medicine
2002-2007	President, German Society of Andrology
since 2007	President, European Society of Endocrinology
since 1965	Scholar of the Studienstiftung des Deutschen Volkes
1990	European Medal and Lecture of the British Endocrine Society (London)
1993	Keith-Harrison-Plaque and Lecture of the Endocrine Society of Australia
1994	Clinical Endocrinology Trust Medal (London)
1994	Fellow of the Royal College of Physicians, London (FRCP)
1996	Ernst-Jung-Prize for Medicine (€ 100.000)
1996	Foreign Member of the Pakistan Academy of Sciences, Islamabad
2001	Clinical Endocrinology Trust (London) Visiting Professorship
2003	Reinier de Graaf Lecture 2003 (Amsterdam)
2005	Premio di Andrologia J. M. Pomerol, Fundació Puigvert (Barcelona)
2005	International Award of Excellence in Published Clinical Research in the Journal of Clinical Endocrinology and Metabolism by the US Endocrine Society (JCEM 2004; 89: 6208-6217) (San Diego)
2006	Doctor honoris causa, Medical University of Łódź (Poland)
2007	"Distinguished Andrologist" of the American Society of Andrology
2007	Honorary Member of the German Society of Urology
2008	Honorary Member of the German Society of Andrology
2008	Honorary Member of the Polish Society of Endocrinology
2008	German Federal Cross of Merit

Over 700 publications in journals, 250 book chapters, editor/coeditor of 10 books.

Married to Susan Nieschlag, born Kritz, two daughters.